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Filed: 12 June 1990

In addition, the Examiner points out the space on page 35, line 31; this is just incorrect spacing.

Applicants acknowledge the Examiner's reminder regarding the requirement for the submission of formal drawings. Applicants are in the process of having formal drawings prepared.

Rejection under 35 U.S.C. § 112, second paragraph.

Claims 18-28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner questions the use of the term "processor". The Examiner's attention is respectfully drawn to page 50, lines 13-15 that outlines that a processor is capable of comparing the input and output signals. The applicants submit that the term is not vague.

The Examiner states that the term "self-assembled monolayer" is vague and indefinite. However, the applicants submit that the term "self-assembled monolayer" (frequently referred to in the art as a "SAM") is well known. As the Examiner is aware, the standard for §112 enablement is that one skilled in the art would be able to use the description of the invention to make and use the claimed invention without undue experimentation. "An inventor need not, however, explain every detail since he is speaking to those skilled in the art." DeGeorge v. Bernier, 226 USPQ 758, 762 (Fed. Cir. 1985). Accordingly, the applicants submit that the term "self-assembled monolayer" is not indefinite as the term is well understood by those in the art.

The term "self assembled monolayer" is a well-recognized term of art for a relatively ordered assembly of molecules. For example, Bamdad et al., (U.S. Patent No. 5,620,850, cited herein with the supplemental IDS) defines "self-assembled monolayer" as:

> a relatively ordered assembly of molecules spontaneously chemisorbed on a surface, in which the molecules are oriented approximately parallel to each other and roughly perpendicular to the surface. Each of the molecules includes a functional group that adheres to the surface, and a portion that interacts with neighboring molecules in the monolayer to form the relatively ordered array.

See column 4, lines 37-45. Additional support for the position that a "self-assembled monolayer"

is a art recogniz d term for a specific typ of structure is found in Bain, et al., (1989) *J. Am. Chem. Soc.*, 111:321-335, discussing the formation of "mixed monolayers" (see abstract) accompanied by the schematic pictures shown in Figure 1 (cited herein with supplemental IDS). See also Bain et al., (1989) *J. Am. Chem. Soc.* 111:7155-7164, discussing the generation of monolayers exposing more than one functional group at the surface (cited herein with supplemental IDS). Whitesides and Laibinis (1990) *Langmuir* 6:87-96, discussing the preparation of self-assembled monolayers and schematic pictures illustrating self-assembled monlayers (cited herein with supplemental IDS). Nuzzo et al., (1983) *J. Am. Chem. Soc.* 105:4481-4483, describing a technique for preparing supported, oriented monolayers of polyfunctional organic molecules (cited herein with supplemental IDS).

Accordingly, the applicants submit that the term "self-assembled monolayer" is known in the art and thus the rejection should be withdrawn.

Claim 22 has been rejected as vague in the recitation of the conductive oligomer formula. Applicants submit that the recitation of "conductive oligomer" is not vague.

The applicants respectfully remind the Examiner that an applicant may be his or her own lexicographer, defining terms as he or she wishes (see Intellicall, Inc. v. Phonometrics, Inc., 21 USPQ 2d 1383 (Fed. Cir. 1992)). 35 U.S.C. §112, second paragraph, requires the claims particularly point out and distinctively claim the subject matter which the applicant regards as his invention.

Applicants respectfully point out that page 22, lines 4-21 defines B and D as follows when g is 1:

> When g is 1, B-D is a conjugated bond, preferably selected from acetylene, alkene, substituted alkene, amide, azo, -C=N- (including -N=C-, -CR=N- and -N=CR-), -Si=Si-, and -Si=C- (including -C=Si-, -Si=CR- and -CR=Si-).

Thus, as defined in th specification on page 22, when g is 1, "B-D" represents either a double bond or a triple bond. The atoms (i.e., B and D) on either side of the double or triple bond may be

carbon-carbon, carbon-nitrogen, carbon-silicon or silicon-silicon. See sp cification pag 22, lines 20-21.

Accordingly, the applicants submit that the use of the phrase "conductive oligomer" is not indefinite as the term is defined in the specification. The rejection of record should be withdrawn.

Rejection under 35 U.S.C. § 103(a)

As discussed in the interview, the present invention is directed to the detection of analyt s using a biosensor. Detection in this system is based on the fact that at least one redox property of a redox active molecule may be altered as a result of its association with a target analyte. The change in the redox property of the redox active molecule as a result of association with an analyte alters the faradaic impedance of the system. This alteration in the faradaic impedance of the system results in a detectable signal.

Systems relying on changes in faradaic impedance can be distinguished from prior art systems on the basis of the use of mediators. That is, prior art systems usually rely on the use of soluble mediators to shuttle electrons between the redox active molecule and the electrode. In the present invention changes in faradaic impedance are done by initiating electron transfer, usually by the application of an input signal, voltage being preferred. Electrons are transferred directly between the redox active molecule and the electrode. See the specification at page 38, lines 14-34.

Thus, the present invention provides a biosensor for the detection of target analytes. The biosensor comprises electrodes, a self-assembled monolayer and a binding ligand covalently attached to an electrode(s) via a spacer, such as a conductive oligomer.

Claims 18-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over Vreeke (U.S. Patent No. 5,534,132), and O'Daly (U.S. Patent No. 5,391,272) in view of Kossovsky (U.S. Patent No. 5,585,646).

Vreeke et al. is directed to providing a standard electrochemical analyte sensor that is

used for competitive assays. The sensor d scribed in Vreeke is comprised of an electrode covered with a hydrogel containing a selective binding unit (SBU) and a redox compound (i.e. the mediator). A labelled complement to the SBU (i.e. a labelled target or target analog) is added to the sensor and binds to the SBU. Upon addition of the sample containing the unlabeled target, the unlabelled target competes off the labelled analog, resulting in a loss of signal. See Column 3, lines 30-34, column 5, lines 17-62 and figure 9.

As acknowledged by the Examiner, Vreeke et al. does not teach a self-assembled monolayer or a conductive oligomer spacer. In addition, the binding ligand of Vreeke is not covalently attached to the electrode. Additionally, Vreeke et al. does not teach or suggest arrays. Further, the method of detection in Vreeke is via a competitive process, i.e., an unknown concentration of target analyte free in solution is allowed to compete with electrode-immoblilized analyte for a limited number of enzyme labeled complement molecules. See Column 5, lines, 40-52.

O'Daly et al. is directed to an immunosensor for the detection of an analyte. The sensor in O'Daly is comprised of an analyte binding agent bound to an electrode and an analyte-enzyme conjugate bound to the analyte binding agent as part of a catalytic electrical circuit. Displacement of the conjugate by analyte causes a decrease in current. See abstract.

As acknowledged by the Examiner, the O'Daly reference does not disclose self-assembled monolayers, a conductive oligomer spacer, or the use of faradaic impedance to detect analytes.

Kossovsky et. al., describe bioelectronic devices in which a layer of electronically active biochemical material is bound to the surface of a semiconductor substrate via a stabilization layer comprising an oligomer. First of all, there is no evidence in Kossovsky that this oligomer forms a "self -assembled monolayer" as is known in the art. Secondly, this oligomer is coated on the semiconductor, not covalently bound as required in the present invention. Thirdly, the biochemical layer is also non-covalently bound to the oligomer. Kossovsky et al. teach that modification in surfaces of semiconductors can impact their electrical performance. However,

neither the teachings of Kossovsky or references cited within disclose th use of s miconductors as biosensors for the detection of analytes in biological samples. That is, there is no detection of target analytes, no SAM, no binding ligand, and no arrays in Kossovsky.

To establish a *prima facie* case of obviousness three criteria must be met: i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; ii) there must be a reasonable expectation of success; and iii) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) M.P.E.P. §2143.

None of the references, taken alone or in combination, provide the motivation to combin the references. None of the references suggest the use of a SAM. In fact, in Vreeke and O'Daly, the use of a SAM would interfere with the interaction of the mediator and the electrode. As the Examiner is aware,

> If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.

See M.P.E.P. §2143.01.

In addition, applicants submit that Kossovsky is non analogous art. "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992); M.P.E.P. § 2141.01(a).

Applicants submit that semiconductors are not in the field of applicant's endeavor. Semiconductors are crystalline materials that variably exhibit electrical conductivity and are used to fabricate solid-state electronic devices. In contrast, the present invention is directed to the

development of biosensors for the detection of the pr sence of specific substances in fluids and gases. Kossovsky is not directed to a sensor. Furthermore, the problem with which Kossovsky is concerned, i.e., modifying the surface of semiconductors, is not relevant to the development of a biosensor. Accordingly, applicants submit that Kossovsky is non analogous art and thus cannot provide motivation to practice the invention.

Furthermore, even assuming, arguendo, that motivation to combine the references exists, there is no reasonable expectation of success at arriving at the present invention by combining these references. None of the references suggest that a sensor that relies on changes in faradaic impedance to detect biomolecules could be developed.

Finally, in the present case, the prior art, alone or in combination, does not disclose each of the claimed elements. Neither Vreeke, O'Daly, or Kossovsky disclose the use of self-assembled monolayers, covalently attached conductive oligomer spacers, or the use of faradaic impedance to detect the binding of an analyte. Moreover the device disclosed in Kossovsky is not a biosensor. Therefore, the requirement of teaching or suggesting all the claim elements has not been met.

Thus, Applicants respectfully assert that Vreeke, O'Daly and Kossovsky either alone or in combination, do not support a conclusion of obviousness. Applicants respectfully request the rejection be withdrawn.

Claims 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al., U.S. Patent No. 5,972,199 and Skotheim et al., U.S. Patent No. 5,089,112, in view of Kossovsky et al., U.S. Patent No. 5,585,646.

Heller and Skotheim are directed to a broad class of biosensors used primarily in glucose sensing for diabetics. These systems are briefly described as follows. A redox enzyme, such as glucose oxidase oxidizes its substrate glucose to produce a product (generally H_2O_2) that either directly or indirectly oxidizes a m diator that then is free to diffuse to the lectrode surface where it is reduced, completing the cycle. Thus, these systems generally utiliz a) an enzyme that

produces a product; b) an electrode; and, c) a mediator that can transf r the electrons between the electrode and the enzyme product, allowing detection.

Heller et al., teach the coating of the glucose sensing surface with a catalyst containing layer that oxidizes contaminants in biological samples before they reach the sensing surface. The sensing surface is a standard surface that requires a redox enzyme to act on the analyte and a mediator to shuttle electrons from enzyme to electrode.

Skotheim et al., teach the use of a mediating species chemically bound to a flexible polymer which can rapidly transfer electrons, is bound in such a fashion as to prevent it from diffusing away from the electrode surface and is relatively insensitive to the presence of interfering substances, such as oxygen.

As acknowledged by the Examiner, neither Heller or Skotheim teach the use of self-assembled monolayers and conductive oligomers. In fact, as outlined above for Vreeke and O'Daly, the use of self-assembled monolayers in the systems described by Heller and Skotheim would interfere with the interaction of the mediator with the electrode.

As stated previously, Kossovsky et al., teaches the use of bioelectronic devices in which the surface of a semiconductor is modified to preserve the activity of biochemical molecules.

Based on the three criteria for establishing a *prima facie* case of obviousness, none of the references, taken alone or in combination, provide the motivation to combine the references. None of the references suggest the use of a SAM. In fact, in the systems described by Heller and Skotheim, the use of SAM would interfere with the interaction of the mediator and the electrode. To paraphrase what was stated above, the use of a SAM would render the inventions taught by Heller and Skotheim unsatisfactory for their intended purposes. Accordingly, there is no motivation to make the proposed modification. See M.P.E.P. § 2143.01.

As argued previously, Kossovsky is non analogous art and not relevant to the development of a biosensor. Accordingly, applicants submit that Kossovsky is non analogous art and cannot provide motivation to practice the invention.

Furth rmore, even assuming, arguendo, that motivation to combine the references exists, there is no reasonable expectation of success at arriving at the present invention by combining these references. None of the references suggest that a sensor that relies on changes in faradaic impedance to detect biomolecules could be developed.

Finally, in the present case, the prior art, alone or in combination, does not disclose each of the claimed elements. Niether Heller, Skotheim, or Kossovsky disclose the use of self-assembled monolayers, covalently attached conductive oligomer spacers, use of an AC/DC voltage source, or the use of faradaic impedance to detect the binding of an analyte. Morever, the device disclosed in Kossovsky is not a biosensor. Therefore, the requirement of teaching or suggesting all of the claim elements has not been met.

Thus, applicants respectfully assert that Heller, Skotheim and Kossovsky either alone or in combination, do not support a conclusion of obviousness. Applicants respectfully request the rejection be withdrawn.

Claims 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Delamarche et al. (1996) *Langmuir*, 12:1997-2006, in view of Kossovsky et al., U.S. Patent No. 5,585,656, in view of Gafni et al., (1996) *Chem. Eur. J.*, 2:759-766.

Delmarche teaches a method of immobilizing antibodies on a self-assembled monolayer by creating a photoactive surface on the self-assembled monolayer. Delmarche et al., disclose the making of a self-assembled monolayer, photoactivation of the monolayer, attachment of a primary antibody, followed by the addition of a secondary antibody conjugated to an enzyme and optical detection using the enzyme. There is no suggestion or teaching in Delmarche that electrodes, a voltage source, or that changes in faradaic impedance can be used to detect biomolecules.

Gafni et al., teach a biosensor using AC-impedance spectroscopy. Gafni et al., suggest that this biosensor is superior to detection systems which rely on electron transfer. See page 760. The biosensor taught by Gafni is a basic capacitance sensor.

As stated previously, Kossovsky et al., teaches the use of bioelectronic devices in which

the surface of a semiconductor is modified to preserve th activity of biochemical molecules.

Based on the three criteria for establishing a *prima facie* case of obviousness, none of the references, taken alone or in combination, provide the motivation to combine the references. None of the references suggest the use of changes in faradaic impedance to detect biomolecules.

In Delmarche, there is no suggestion that electrodes or a voltage source can be used to detect an analyte. In fact, Delmarche teaches optical detection of an analyte and thus does not provide motivation to practice the invention.

As argued above, Kossovsky is not relevant to the development of a biosensor and thus cannot provide motivation to practice the invention.

Furthermore, even assuming, arguendo, that motivation to combine the references exists, there is no reasonable expectation of success at arriving at the present invention by combining these references. None of the references suggest that a sensor that relies on changes in faradaic impedance to detect biomolecules could be developed.

Finally, in the present case, the prior art, alone or in combination, does not disclose each of the claimed elements. Neither Delmarche, Gafni, or Kossovsky disclose the use of faradaic impedance to detect the binding of an analyte, a conductive oligomer spacer, or arrays. Moreover, the device disclosed in Kossovsky is not a biosensor. Therefore, the requirement of teaching or suggesting all the claim elements has not been met.

Thus, applicants respectfully assert that Delmarche, Gafni and Kossovsky either alone or in combination, do not support a conclusion of obviousness. Applicants respectfully request the rejection be withdrawn.

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If after review, the Examiner feels there are further unresolved issues, the Examiner is invited to call the undersigned at (415) 781-1989.

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The Commission r is authorized to charge any additional fees, including any extension fees, which may be required, or credit any overpayment to Deposit Account No. 06-1300 (Our Order No. A-64559-3/RFT/RMS/RMK).

Dated: 5/22/00

Respectfully submitted,

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Appendix of Pending Claims

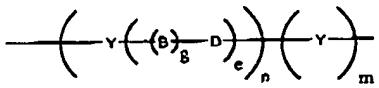
18. (Amended) An apparatus for the detection of a non-nucleic acid target analyte in a test sample, comprising:
a) a test chamber comprising at least a first and a second measuring electrode, wherein said first measuring electrode comprises:
I) a self-assembled monolayer; and
ii) a binding ligand covalently attached to said electrode via a spacer; and
b) a voltage source electrically connected to said test chamber.

19. (Amended) An apparatus according to claim 18 or 20 further comprising a processor.

20. An apparatus for the detection of a non-nucleic acid target analyte in a test sample, comprising:
a) a test chamber comprising an array of first measuring electrodes each comprising:
i) a self-assembled monolayer; and
ii) a binding ligand covalently attached to said electrode via a spacer;
wherein said test chamber further comprises at least one second measuring electrode; and
b) a voltage source electrically connected to said test chamber.

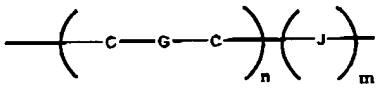
21. An apparatus according to claim 18 or 20 wherein said spacer is a conductive oligomer.

22. An apparatus according to claim 21 wherein said conductive oligomer has the formula:



wherein
Y is an aromatic group;
n is an integer from 1 to 50;
g is either 1 or zero;
e is an integer from zero to 10;and
m is zero or 1;
wherein when g is 1, B-D is a conjugated bond; and
wherein when g is zero, e is 1 and D is preferably carbonyl, or a heteroatom moiety, wherein the heteroatom is selected from oxygen, sulfur, nitrogen, silicon or phosphorus.

23. An apparatus according to claim 21 wherein said conductive oligomer has the formula:



wherein
n is an integer from 1 to 50;
m is 0 or 1;
C is carbon;
J is carbonyl or a heteroatom moiety, wherein the heteroatom is selected from the group consisting of oxygen, nitrogen, silicon, phosphorus, sulfur; and
G is a bond selected from alkane, alkene or acetylene, wherein if m = 0, at least one G is not alkane.

24. An apparatus according to claim 18 or 20 wherein said spacer is an insulator.

25. An apparatus according to claim 18 or 20 wherein said self-assembled monolayer comprises insulators.

26. An apparatus according to claim 18 or 20 wherein said self-assembled monolayer comprises conductive oligomers.

27. An apparatus according to claim 18 or 20 wherein said self-assembled monolayer comprises insulators and conductive oligomers.

28. An apparatus according to claim 18 or 20 wherein said binding ligand is a protein.